The Shifting Treatment Landscape for Alzheimer's Disease in Primary Care

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doi:10.12788/fp.0640

KEY TAKEAWAYS

- Alzheimer's disease (AD) is a common, progressive neurodegenerative disease that is frequently underdiagnosed and misdiagnosed.
- Delays in accurate diagnosis and management of AD can place an unnecessary burden on patients and their families.
- Primary care providers and primary care geriatricians are often the first to encounter patients with cognitive impairment, playing an essential role in the timely diagnosis and management of AD.
- Biomarker testing, which is increasingly available in care settings, can help reduce misdiagnosis of AD and determine eligibility for disease-modifying therapy.
- Treatment of AD is based on the stage of disease and may include amyloid-targeting therapies for patients with mild cognitive impairment or mild dementia due to AD.

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ACKNOWLEDGMENT

Editorial support was provided by Austin Ulrich, PharmD, BCACP, at Primary Care Education Consortium.

DISCLOSURES

Dr. Davis serves as a member of the advisory board and speakers bureau of Eli Lilly. Dr. Obisesan serves as a member of the advisory boards of Eli Lilly and Eisai Pharmaceuticals.

SUPPORT

This activity is sponsored by Primary Care Education Consortium and funded by a grant from Eli Lilly and Company.

INTRODUCTION

Alzheimer's disease (AD) is a chronic, progressive neurodegenerative disease affecting cognition, behavior, and function, and its neuropathologic hallmarks are usually present decades before symptoms are evident.[1–3] AD is a highly prevalent disease in the United States (US) with a continually increasing healthcare challenge as the size of the aging population grows.[1] The population of Americans aged 65 years and older is projected to grow from 58 million in 2022 to 82 million in 2050, accompanied by a higher number and proportion of individuals with AD and other dementias, since the risk of dementia increases with advancing age.[1] Mortality rates are higher in people with AD, and AD is the fifth-leading cause of death for people in the US aged 65 years and older (2021 data).[1] Along with other dementias, AD has a high disease burden in the US, including effects on psychosocial aspects of patients' quality of life and significant direct and indirect costs, with an estimated $360 billion spent on healthcare and long-term care annually.[1]

AD progresses along a continuum that begins with preclinical AD, where neuropathologic changes are present without cognitive impairment, and progresses to a clinical presentation that includes mild cognitive impairment (MCI), mild dementia, and eventually moderate and severe dementia.[2] Several different staging systems describe the progression of AD, with variations in nomenclature but overall similarities with regard to pathophysiology and neurologic deficits.[2,4,5] Symptoms become evident in the MCI phase of the AD continuum, characterized by subtle cognitive and functional changes that may only be noticeable to the patient, family members, friends, and care partners.[1] AD pathology can be detected much earlier than symptoms and can establish the etiology of the symptoms. For example, amyloid plaque deposition can occur up to 20 years before the onset of cognitive symptoms.[4,6] Tau pathology may be detected in preclinical AD in the form of soluble P-tau protein, and neurofibrillary tangles (NFTs) may be detected with tau positron emission tomography (PET) closer to symptom onset. Both amyloid and tau are pathologic hallmarks of AD.[1,4,6] Despite the substantial and increasing burden of AD, the condition remains underdiagnosed in many clinical settings, including primary care.[1] Outside of research, a high proportion of patients who meet the diagnostic criteria for AD are not diagnosed. Per claims data, of those patients covered by Medicare with a diagnosis of AD or other dementia, only half of these patients reported that they were informed of their diagnosis by their clinician.[1] Misdiagnosis can result in potential harms, necessitating a change in approach to early evaluation and diagnosis of AD.[1]

The role of PCPs and geriatricians in AD care

The aging population and increase in older patients overall create an urgent need for better identification, management, and treatment of AD. Due to a shortage of AD specialists, it often falls to primary care providers (PCPs) to care for patients with MCI and AD.[1] Patients with early signs of dementia or AD often present first to their PCP or primary care geriatrician, who can help detect, diagnose, and manage MCI or mild dementia due to AD.[7] These providers serve a critical role in starting a timely assessment of MCI or mild dementia due to AD, initiating shared decision-making for referrals and treatment decisions, partnering in monitoring patients started on amyloid-targeting therapies (ATTs), and supporting patients and care partners throughout the care journey.

Patients and care partners often share their concerns for cognitive impairment with clinicians during routine and preventive care visits like the annual wellness visit (AWV), and clinicians and their staff may observe cognitive or behavioral changes during these visits. Prompt follow-up assessment is required.[7] However, non-dementia trained clinicians, and even AD specialists, may miss this critical opportunity to initiate investigation of this concern.[7,8] Clinicians may continue the AD work-up, ruling out other conditions or diseases, or they can refer the patient to AD specialists, such as dementia-trained neurologists, psychologists, or geriatricians.[2]

CASE STUDY

A 72-year-old woman with past medical history of hypothyroidism and hypertension controlled with medication presents to her primary care clinic with her husband, who voices concerns that she seems to be forgetting more and more things over the past year. She has missed paying utility bills and routine hair appointments. She is also experiencing agnosia, having trouble recalling names of familiar locations and objects.

The patient in this case scenario is experiencing cognitive impairment; therefore, MCI or mild dementia due to AD should be included in the differential diagnosis. Her PCP ordered basic labs to rule out potential underlying metabolic concerns (including B12 and thyroid-stimulating hormone). Rapid plasma reagin and human immunodeficiency virus (HIV) were not ordered due to the patient not having risk factors for neurosyphilis or HIV-associated dementia, respectively. The PCP reviewed and reconciled the patient's dosage and scheduling of medications and supplements to minimize iatrogenic effects on cognition using the Beer's list as a reference.[9] As patients age, the metabolism of medications may be impaired and medications may build up, potentiating toxic effects. The PCP also performed depression and hearing assessments during the routine exam, which were negative, and a validated cognitive assessment, which was positive for impairment. Finally, the PCP ordered magnetic resonance imaging (MRI) for structural evaluation of the brain to rule out potential acute non-AD factors.

WHO SHOULD BE EVALUATED FOR COGNITIVE IMPAIRMENT?

Historically, cognitive impairment testing has not been systemically initiated or addressed for all patient groups.[10] Detecting possible cognitive impairment in clinical settings can help identify patients who warrant further cognitive testing and evaluation.[11] The following individuals should be evaluated for cognitive impairment and potentially further AD testing[11]:

- Patients with memory concerns or other cognitive complaints, such as changes in personality, depression, unexplained worsening of chronic disease, and falls or balance issues
- Patients whose care partner or family reports cognitive impairment, with or without patient concurrence
- Medicare beneficiaries, as part of the AWV
  - The 3 billing codes for AWVs, which are built into many electronic medical record systems, are G0402, G0438, and G0439[12]
- Even though the United States Preventive Services Task Force has not provided guidance on cognitive assessments for adults aged 65 years and older, many geriatric-trained providers routinely assess all their patients annually or every 6 months

Despite cognitive assessment being a standard component of AWVs for patients with Medicare, only 16% of patients aged 65 years and older reported receiving a brief cognitive assessment regularly.[13] PCPs should consider routinely screening patients at risk for AD with one of several tools validated for use in primary care settings.[2] Five of the tools, each of various sensitivity, are described below; they are available online.

Mini-Mental State Examination (MMSE). The MMSE is a 30-item instrument administered to the patient, and it takes about 5-10 minutes to complete.[2,14] This tool is sensitive and reliable for detection of memory and language deficits but may not capture impaired executive functioning.[15]

Montreal Cognitive Assessment (MoCA). The MoCA is a 12-item assessment that takes about 10 minutes to complete.[2] This tool was originally developed to improve detection of MCI, and thus, it is more sensitive than the MMSE for evaluating visuospatial abilities, language, memory, and executive function.[15,16] Of note, clinicians are required to receive training and certification to administer the MoCA.

Mini Cognitive Assessment Instrument (Mini-Cog). This brief evaluation consists of a 3-item recall and clock drawing that is administered to the patient and takes about 2-3 min-

utes to complete.[2] This assessment requires no training, and the results are easy to interpret, though it may not capture very subtle changes.[2]

AD8 Dementia Screening Interview (AD8). This short, 2-to-3-minute, 8-item tool is usually administered to an informant to help detect dementia in patients based on the informant's responses.[2] Some experts suggest that the AD8 may be administered to patients in the absence of an informant with similar results, especially in patients with mild dementia.[17]

Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE). The IQCODE is another questionnaire designed to be administered to an informant, and it takes about 10 minutes to complete.[2,18]

Clinicians should be sensitive to patients who may have low health literacy and those who are affected by health disparities and other socioeconomic and psychosocial factors that may prevent access to testing or affect the process of evaluating cognitive impairment. If AD is suspected, the next step to support a diagnosis of AD is consideration and assessment of neuropathologic etiology.[1]

AD ETIOLOGY

AD is characterized by 2 underlying neuropathologic hallmarks: amyloid plaques and tau neurofibrillary tangles (NFTs). Extracellular beta-amyloid plaques and intracellular NFTs accumulate over time, leading to progressive neurodegeneration, synaptic dysfunction, and inflammation. Amyloid plaques form 10-20 years before symptom onset, whereas NFTs develop 5-10 years before cognitive symptoms.[1,2,4]

Historically, before progress in biomarkers, the diagnosis of AD was considered either clinical (using primarily clinical data) or neuropathologic (formulated post-mortem by visualizing corresponding neuropathologic changes). However, recent guidance supports the concept of a clinical-neuropathologic diagnosis.[3,5] Hence, an accurate diagnosis of AD requires both a clinical and biomarker evaluation, including detailed medical and social history (risk factors), patient symptoms, cognitive assessment, physical examination findings, laboratory testing, and possibly imaging to identify neuropathologic changes.[3]

The differential diagnosis in evaluating patients who present with symptoms suggestive of AD may be challenging, though AD is no longer diagnosed by symptomatology alone. Biomarker testing can help differentiate conditions that may have a clinical presentation like AD, especially with effects on cognition. Examples include other neurodegenerative diseases (such as Parkinson's disease or dementia due to vascular disease), insomnia, depression, excessive alcohol use, and use of certain medications. Nevertheless, AD is the most common cause of dementia, accounting for an estimated 60% to 80% of cases.[1] Vascular dementia accounts for 5% to 10% of cases, an estimated 5% of patients have dementia with Lewy bodies, and Parkinson's disease dementia accounts for about 3.6% of cases.[1] Additionally, frontotemporal degeneration accounts for about 10% of dementia cases in individuals younger than 65 years of age and about 3% of dementia cases in individuals 65 years of age and older.[1] More than 50% of patients with AD have mixed dementia, and by age 85, 85% of patients with any type of dementia will have a second type.[1]

Due to variable accessibility and specificity of testing, biomarker testing is often conducted after the patient has been referred to an AD specialist; testing may include amyloid PET, cerebrospinal fluid (CSF) analysis, and/or plasma analysis.[3] However, PCPs can order blood-based biomarker tests to help expedite the referral process and diagnosis if comfortable doing so.

Biomarkers in AD

Detection of AD neuropathology and associated neurodegenerative disease through structural imaging and fluid biomarkers has emerged as a key component of the diagnostic work-up.[2,3] The use of biomarker testing in AD can help address the high rates of misdiagnosis, as 25%-30% of patients with a clinical diagnosis of AD were misdiagnosed by dementia specialists. There are even higher rates of misdiagnosis in primary care.[19] Alongside PET imaging, CSF biomarkers and blood-based biomarker tests are options for evaluating cognitive impairment in older adults.[20,21]

Key biomarkers of AD pathology include amyloid beta peptide (Aβ) and phosphorylated tau (P-tau) protein, which are associated with amyloid plaques and neurofibrillary tangles. These biomarkers can be assessed through fluid-based testing (CSF or plasma) and imaging with amyloid PET (**TABLE 1**).[22] Commercially available biomarker tests include US Food and Drug Administration (FDA)-approved amyloid and tau PET. Recently, 3 in vitro CSF diagnostic tests have been authorized for use by the FDA. They are all hybrid ratios with strong concordance to amyloid PET.[23] Multiple plasma tests are commercially available as laboratory developed tests and report performance similar to FDA-cleared CSF assays (**BOX 1**).[22,24,25–30] In a recently FDA-cleared blood biomarker, the ratio of phosphorylated tau to amyloid in plasma is intended to aid in the identification of amyloid pathology in appropriate patients.[26] These tests are not used alone, but with the patients' history and clinical assessments in making an early symptomatic AD diagnosis.[22,27–30]

The accuracy, cost-effectiveness, and accessibility of blood-based biomarkers for AD pathology in AD research and clinical diagnosis have been assessed in multiple studies.[23,31,32] In a study evaluating the use of blood-based biomarkers in primary and secondary care, PCPs had a diagnos-

TABLE 1. Key biomarker tests used in the diagnosis of AD via fluid-based and imaging-based analysis.[22,26]

AD Pathology	CSF	Plasma	Imaging
Amyloid beta proteinopathy	-	-	Amyloid PET
Phosphorylated and secreted tau	-	p-tau217	-
Hybrid ratios	p-tau181/ Aβ 42, t-tau/ Aβ 42, Aβ 42/40	%p-tau217 p-tau217/ Aβ 42	-

Abbreviations: %p-tau217, P-tau217/non-phosphorylated tau217 ratio.

The intended use of these tests is in adult patients, 55 years and older, presenting with cognitive impairment who are being evaluated for AD and other causes of cognitive decline.

BOX 1. Classification of laboratory tests.[24,25]

Laboratory Test	Description	Examples
In vitro diagnostic tests (IVDs)	Used to analyze human samples in local or office laboratories and cleared by the FDA for use	CSF biomarkers
Laboratory developed tests	A subset of IVDs where the samples must be sent to a centralized CLIA-certified laboratory for analysis. They do not need FDA approval for use	Plasma biomarkers

Abbreviations: CLIA, Clinical Laboratory Improvement Amendments of 1988.

tic accuracy of 61% for identifying clinical AD after a standard clinical examination vs 91% with the addition of a blood-based biomarker to the diagnostic work-up.[23] This research clearly demonstrates that incorporating AD biomarkers into a clinical work-up improves the diagnostic accuracy for both primary care and dementia specialists. Variability in coverage of biomarker assessments, inclusive of imaging, CSF analysis, and plasma tests, is a limitation of these approaches in AD detection and diagnosis. The adoption of biomarker tests has historically been relatively low and slow due to challenges with availability, cost, reimbursement, and PCP confidence in interpretation. However, blood-based biomarkers are becoming increasingly available clinically.[33,34]

Genetic testing

Many genetic features affect the risk of AD-related dementia. Of those that increase the risk of AD, ApoE ε4 is known to have the most significant impact on developing late-onset AD dementia.[1] Each individual inherits 1 of 3 alleles of the ApoE gene from each parent— ε2, ε3, or ε4. ApoE ε2 is protective, and those who have the ε2 form of ApoE tend to have onset of AD later in life. ApoE ε3 is the most common isoform and is considered neutral.[35] However, the risk of AD is greater in those carrying the ε4 variant, with highest risk for ApoE ε4 homozygotes vs ApoE ε4 heterozygotes vs non-carriers. It is important to note that while risk is increased in those carrying either 1 or 2 copies of the ε4 allele, ApoE ε4 carriers are not guaranteed to develop AD.[1] ApoE testing is also recommended to assess risk for development of amyloid-related imaging abnormalities (ARIA) associated with ATT treatment, which is discussed in more detail later. Of note, PCPs can order ApoE testing for patients expected to start an ATT to facilitate a more informed discussion of benefit and risk. ApoE testing is not required to begin treatment with ATTs, but it is recommended.[36]

It is also known that a small number of people (1% or fewer of those with AD) develop earlier-onset disease because of mutations to 3 specific genes, including the amyloid precursor protein gene or the genes for the presenilin 1 or the presenilin 2 proteins. These genetic mutations of the amyloid protein are called dominantly inherited or autosomal dominant AD. There are additional genetic risk factors for developing AD, such as Down syndrome. Individuals living with Down syndrome develop AD earlier than the unaffected population.[1] Patients who undergo genetic testing should receive appropriate genetic counseling and guidance regarding accurate interpretation of results.

The next step in helping to establish a diagnosis of AD includes working up the differential diagnosis. PCPs and geriatricians may initiate an evaluation or may choose to defer the evaluation until the patient can see a dementia specialist, expanding the multidisciplinary team of providers. Referrals may occur at different points across the patient's journey among providers to establish a diagnosis. The decision to refer may be based on provider knowledge, availability of dementia specialists, time, and infrastructure of the practice environment or healthcare organization. Cognitive testing and laboratory assessment, including biomarker confirmation of AD neuropathology, are part of the evaluation. Moreover, connecting patients with suspected or confirmed MCI or mild dementia to a dementia specialist promotes a timely and accurate diagnosis of early symptomatic AD and sets the stage to discuss potential treatment options, including disease-modifying therapy.

What happens after a patient has been diagnosed with early symptomatic AD

Following a clinical and biomarker-supported diagnosis of AD, PCPs and geriatricians continue to play a key role in the continuity of care for patients diagnosed with AD and their care partners. PCPs and geriatricians can be involved in dis-

ease monitoring, education, and counseling, as they typically have more frequent touch points with patients than the dementia specialists. Patients often defer to their PCP and primary care geriatrician in complex disease management for support and understanding of subspecialist plans. Monitoring for worsening cognitive function should include cognitive and functional assessments at routine follow-up appointments about every 6-12 months, which can also occur in primary care.[2]

CURRENT APPROACHES TO TREATMENT OF AD

For patients managed in the primary care setting, PCPs can consider how best to disclose the diagnosis to the patient and care partners as well as discuss treatment options and support resources.[2,37] In the event that the patient is no longer able to make informed decisions for themselves, PCPs can encourage patients and care partners to have conversations about advanced care planning.[2] After a diagnosis of AD has been verified by a dementia specialist, treatment can be initiated based on disease stage, patient characteristics, and agreed-upon treatment and life goals for the patient. Additionally, for patients who have trouble coordinating medical visits, a telehealth appointment or the PCP consulting with the dementia specialist may be an option.

Nonpharmacologic therapy

Nonpharmacologic therapies can have a positive impact on the quality of life for patients with MCI and mild dementia due to AD and are relatively safe and inexpensive.[2,14] Possible nonpharmacologic interventions include dietary changes, physical exercise, cognitive training, social interactions with others, adequate sleep, music- and art-based therapies, and proper personal hygiene.[1,14,38] Often, nonpharmacologic therapies are used with the specific aim of reducing behavioral and psychological symptoms, such as depression, apathy, agitation, aggression, sleep disturbances, and wandering.[1] Connecting patients and families with community resources is a critical component of supportive care.

Pharmacologic therapy—symptomatic treatments

Three acetylcholinesterase inhibitors (AChE-I) for symptomatic treatment of AD are currently available for patients diagnosed with Alzheimer's dementia. These agents can provide symptomatic benefit but do not affect the underlying neuropathological changes associated with AD.[1,2,39] An N-methyl-D-aspartate (NMDA) receptor antagonist is also approved for use for moderate or severe AD.[39] A combination acetylcholinesterase inhibitor and an NMDA antagonist is also available.[1] Common side effects of these symptomatic therapies include headaches, nausea, and weight loss.[1] Please note, there are no approved medications with a labeled indication for treatment of MCI.

Pharmacologic therapy—ATTs

ATTs are monoclonal antibodies that can modify the underlying pathology of AD. In clinical trials, they have been shown to slow cognitive and functional decline in patients with MCI or mild dementia, due to early symptomatic AD with evidence of amyloid pathology by reducing amyloid beta plaques, the accumulation of which is a defining feature of AD.[1]

Adverse effects of ATTs include headaches, infusion-related reactions, and ARIA.[1] ARIA is a common side effect that is usually temporary and asymptomatic but can be serious and life-threatening in some cases. It can involve swelling and/or microhemorrhage in some areas of the brain. Patients with ARIA may present with symptoms that mimic an acute stroke, including focal neurologic weakness, dizziness, headache, confusion, nausea, gait difficulty, and vision changes. The term ARIA is inclusive of 2 types of findings on MRI: 1) ARIA-edema (ARIA-E), observed on MRI as vasogenic cerebral edema or sulcal effusion; 2) ARIA-hemosiderin deposition (ARIA-H), which includes microhemorrhage, macrohemorrhage, and superficial siderosis.[40] Managing ARIA may require discontinuing the ATT temporarily or indefinitely. It is recommended that patients undergo ApoE testing before starting treatment with ATTs due to the increased risk for ApoE ε4 carriers of developing ARIA.[1]

When a patient has been started on an ATT, the dementia specialist will monitor the duration of treatment. However, PCPs and non-ATT-prescribing geriatricians can assist with monitoring disease progression via the use of cognitive assessment tools. PCPs and non-ATT-prescribing geriatricians also have an important role in monitoring for potential side effects.[2] Establishing programs or initiatives that encourage collaboration between PCPs and AD specialists can support patients and care partners throughout the care journey.[7] Clear communication between the care team, patients, and care partners is essential for optimal outcomes. Enlisting staff such as patient navigators and social workers may help facilitate the communication and coordination among providers, patients, and their care partners.

CASE STUDY (CONTINUED)

The patient was referred to a dementia specialist. The next step was confirmation of amyloid pathology, which can be performed via PET imaging, CSF biomarker, or blood-based biomarker assessments. Based on the clinical and neuropathologic evidence, the patient was diagnosed with mild dementia due to AD. This diagnosis was shared with the patient, her care partner, and the patient's PCP.

After diagnosis disclosure, the patient, her care partner, and the dementia specialist discussed and considered treatment options. This discussion included consideration of ATTs that may slow the progression of early symptomatic AD.

SUMMARY

This article described the shifting treatment landscape for AD in primary care to provide patient-centered care, with the goal of optimizing patient outcomes. AD is a common, progressive disease that is frequently underdiagnosed and misdiagnosed, resulting in delays in appropriate symptom and disease management. PCPs and geriatricians are often the first to encounter patients with signs and symptoms of cognitive impairment and are critical to a timely and accurate diagnosis and urgent management of AD. The use of biomarker testing, which is becoming increasingly available in more care settings, can help reduce misdiagnosis of AD and determine eligibility for disease-modifying therapy. Treatment of AD is based on the clinical stage of disease and evidence of amyloid neuropathology. The use of biomarker testing may augment the ability to help patients earlier in the symptomatic stages and provide the opportunity for treatment. Treatment of MCI and mild dementia due to AD with evidence of amyloid pathology may involve ATTs. Understanding the shifting paradigm may aid PCPs and geriatricians in managing their patients living with MCI and mild dementia due to AD. ●

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